Secondary malignancy risk in patients treated with proton versus photon radiation: a review of the data

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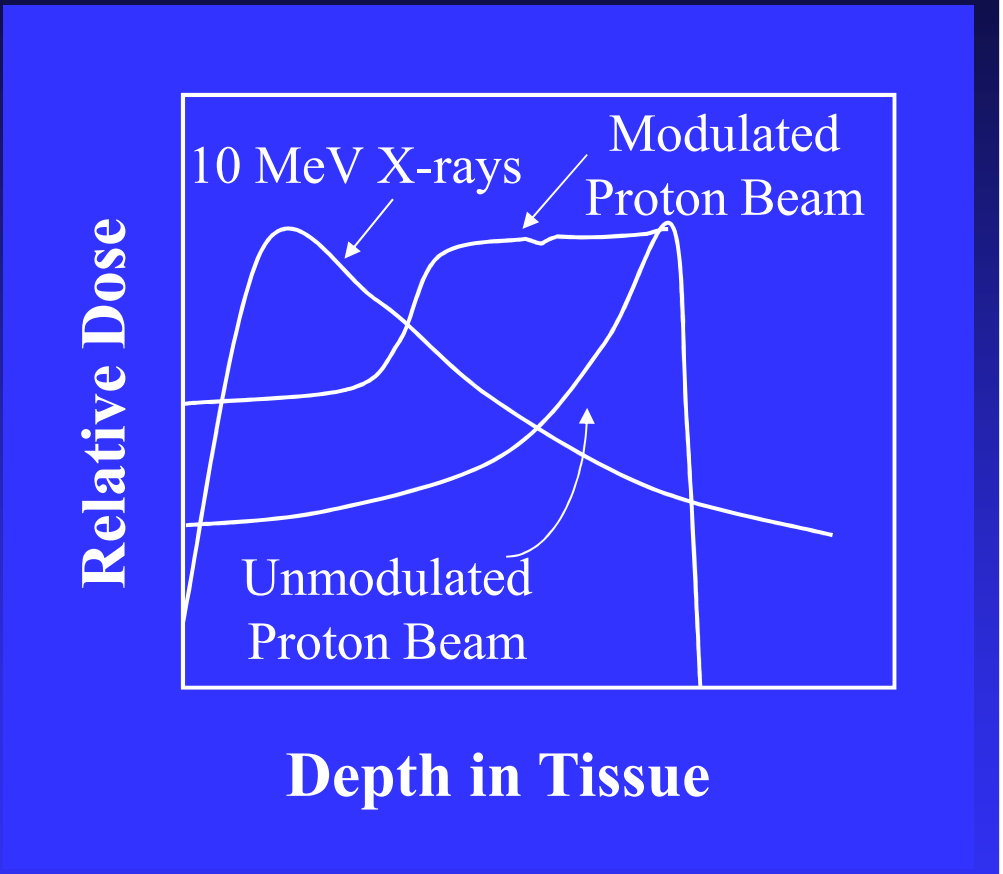
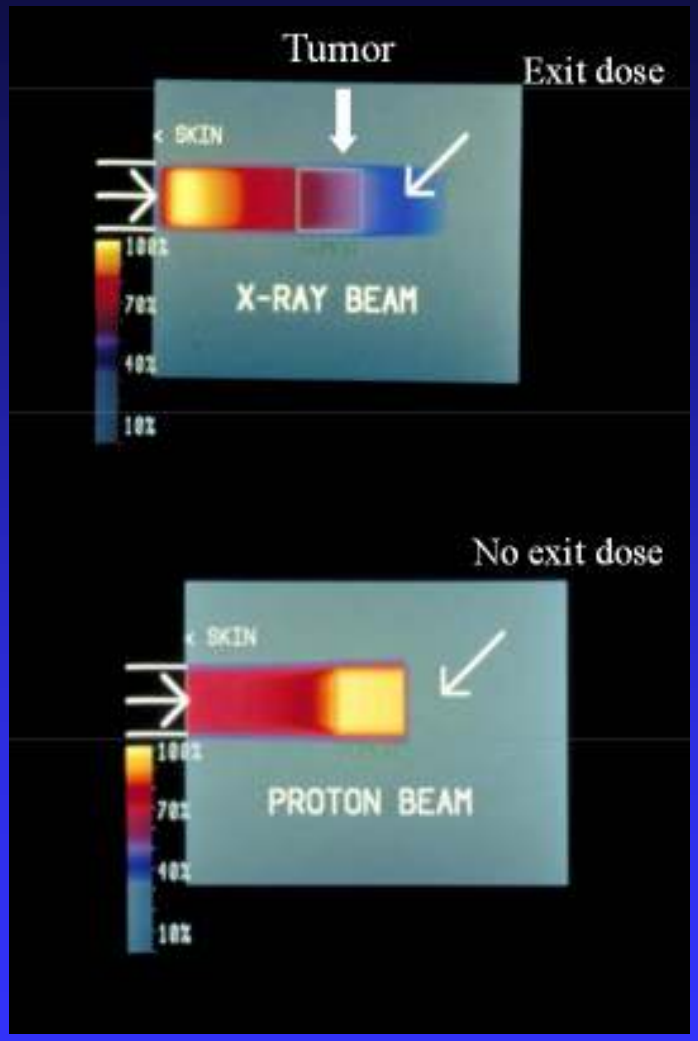
Why protons are advantageous in radiotherapy

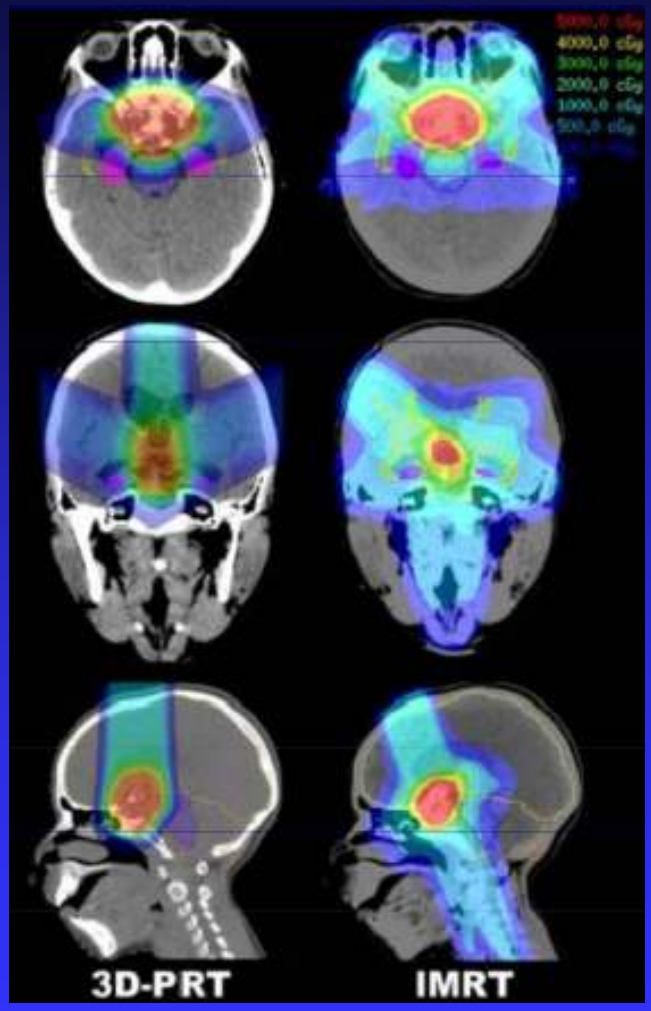
- Relatively low entrance dose
- Maximum dose at depth depending on the energy protons (Bragg peak !)
  ➔ Tumour location
- Energy modulation for broadening maximum
  ➔ Spread out Bragg peak (SOBP)
- Rapid distal fall-off
  ➔ Sparing distal normal tissues



Comparison dose distribution protons versus x-rays



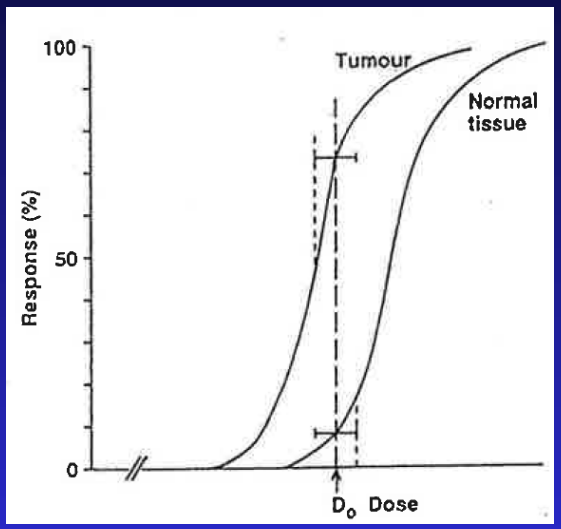
Homogeneous phantom



paediatric craniopharyngioma

(A.K. Lee, MD Anderson Hospital)

- Dose to tumour surrounding normal tissues lower in proton therapy than IMRT



➔ Risk for acute & late radiotoxic side effects lower in proton therapy

- Dose to rest of the body from stray secondary radiation ?

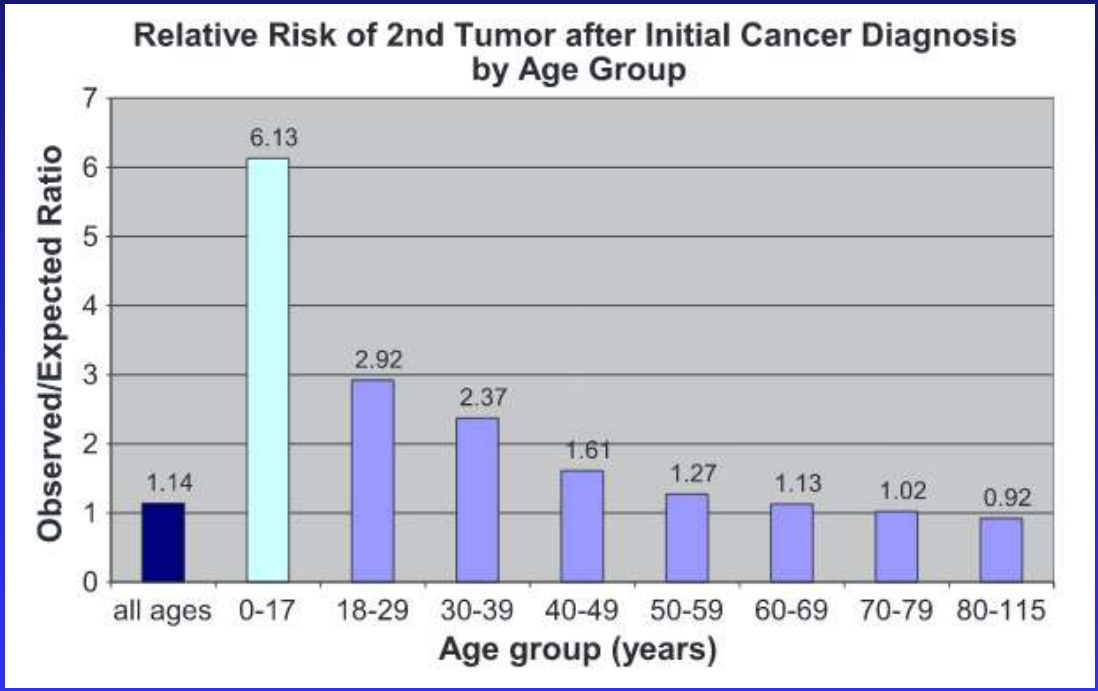
➔ IMRT : predominantly photons scattered in linac head and in patient in x-ray based RT with comp photoneutrons for high energy MV therapy

➔ Protons: predominantly secondary neutrons related to nuclear reactions (p,p'n) (p,2p'n) with materials in treatment head and patient

Issue of secondary cancer risk in proton therapy versus IMRT

Secondary neoplasms by age group at diagnosis

- **Relative risk of secondary tumor after initial cancer diagnosis in patients treated with photon RT by age group according to the SEER (Surveillance, Epidem and End Results program) US cancer registries (Curtis NIH 2006)**

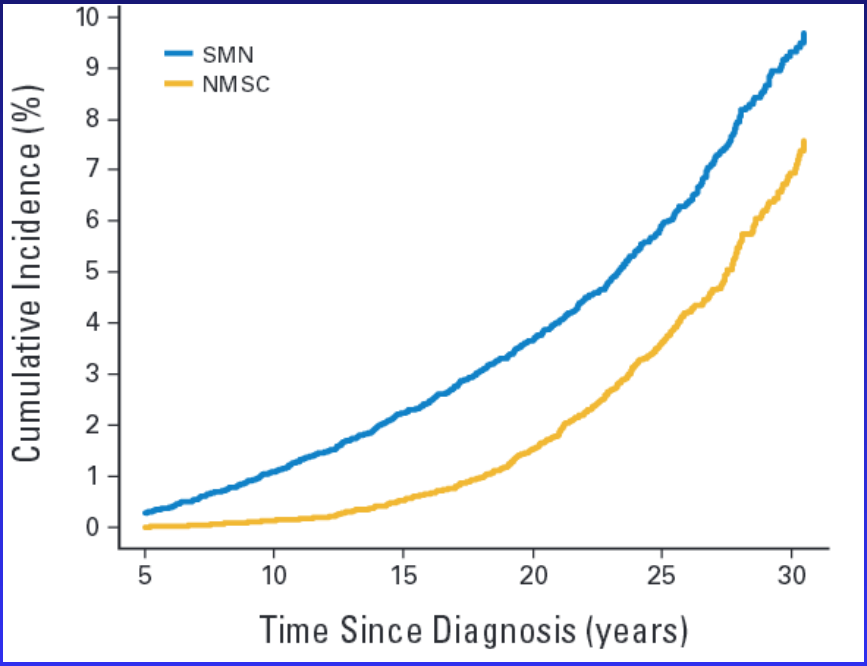


➔ **Observed versus expected ratio of secondary cancers versus age of diagnosis**

➔ **Issue of secondary cancer especially important for paediatric patients !!**

Secondary neoplasms after radiotherapy x-rays in childhood

- Secondary neoplasm incidence data of the childhood Cancer Survivor Study (CCSS) cohort (age at treatment younger than 21 years) treated with photon RT between 1970 and 1986 (Meadows J Clin Onc 2009)



- Data secondary neoplasms (SMN) and non-melanoma skin cancer (NMSC)
  ➔Breast ca, thyroid ca, CNS, sarcoma, leukemia, lymphoma e.a.
- 60-80 % developed in radiation field, 20 % completely out of field (>5 cm)

Secondary neutrons in clinical proton radiotherapy:
A charged issue

David J. Brenner*, Eric J. Hall

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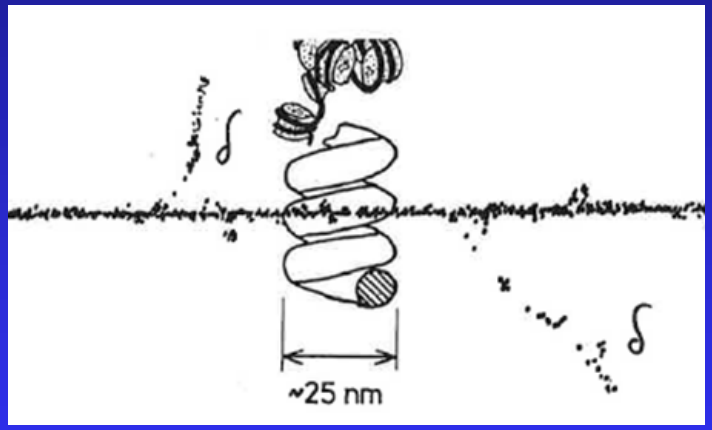
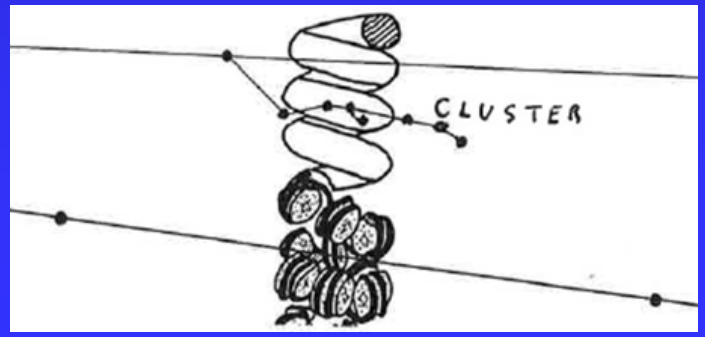
- **Proton therapy: secondary neutrons**
  high LET radiation

  → **complex DNA damage**

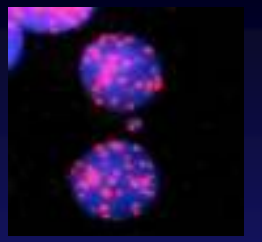


- **Photon therapy: scattered photons**
  low LET radiation

  → **simple single strand DNA breaks**
  and double strand DNA breaks



Relative Biological Effectiveness (RBE)



- Definition RBE

$$\text{RBE} = \frac{\text{Dose (Gy) Co60 } \gamma \text{ rays required for effect}}{\text{Dose (Gy) radiation type required for effect}}$$

- Example: RBE for $^{9}Be(14.5\ MeVd,n)^{10}B$ neutrons for mutagenic effects scored by micronucleus assay in lymphocytes (Vral et al. 1997)

^{60}Co-γ rays

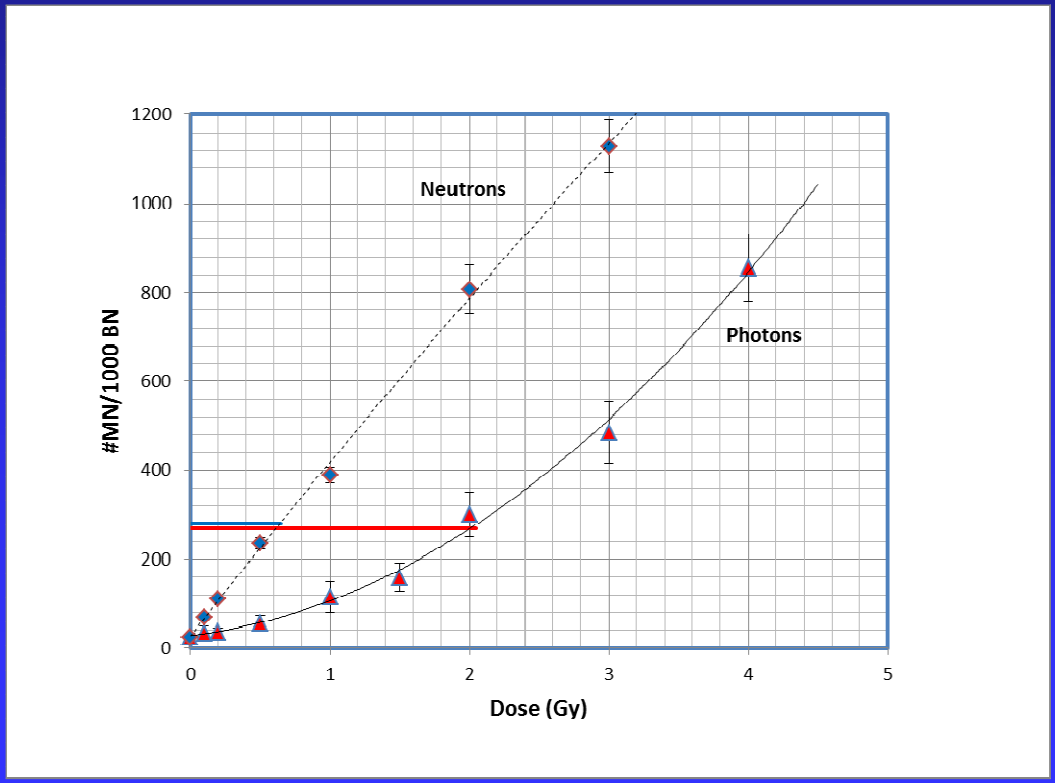
fit: $MN=0.027+0.049D+0.039D^2$

neutrons

fit: $MN=0.027+0.370D$

➔ RBE = 3.4 for 2 Gy

➔ RBE = 7.5 for low dose

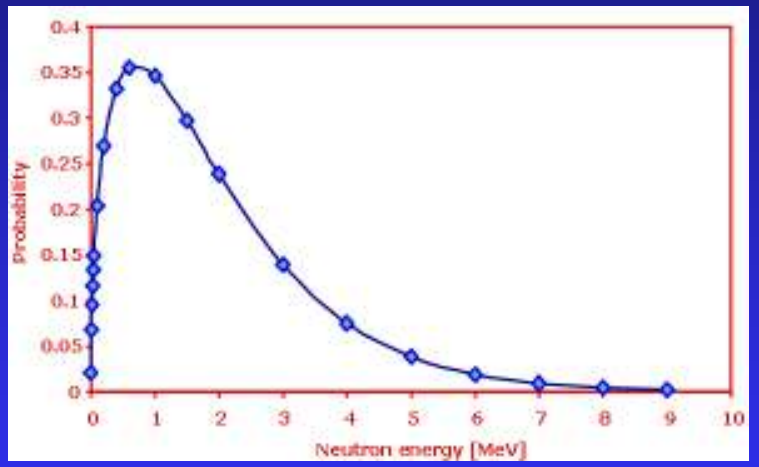


RBE of neutrons

- **Most data are available for fission neutrons (produced in nuclear reactors and atomic bomb radiation) with energy spectrum maximum at 1 MeV**

Table: low dose RBE overview for fission neutrons (ICRP 92 2003)

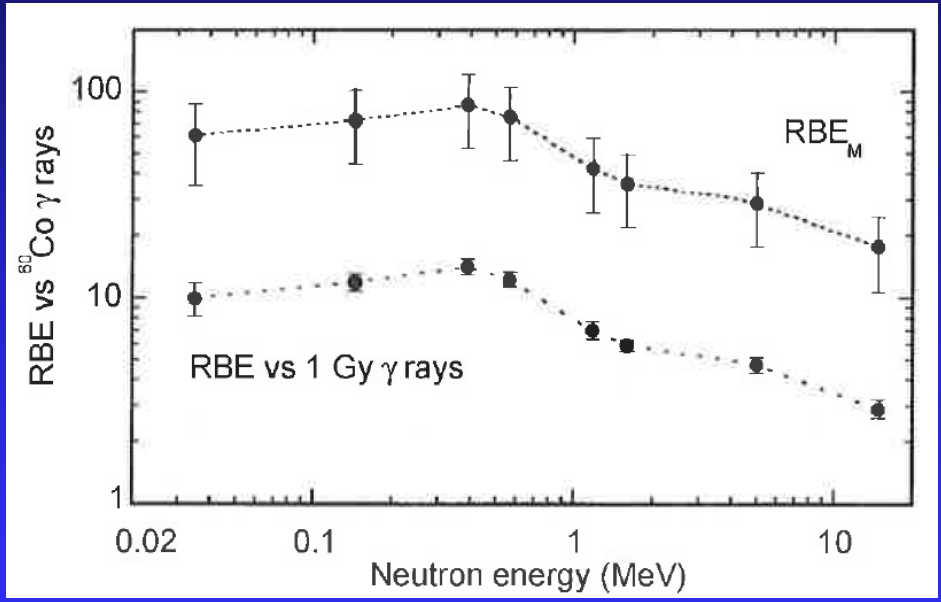
Endpoint	RBE
A-bomb data cancer incidence	**63**
Carcinogenesis in mice	30 (6-59)
Dicentric chromosome aberrations	38-53
In vitro neoplastic transformation	10-35

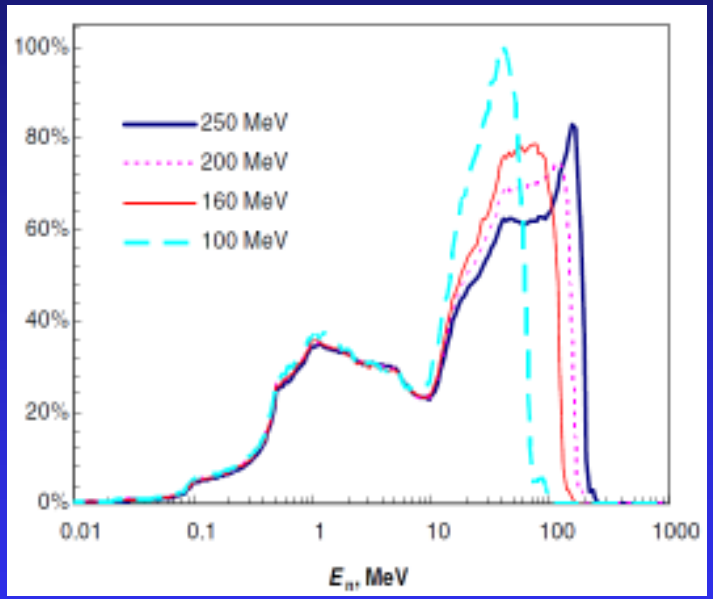


➔ **RBE for mutagenesis and carcinogenesis for fission neutrons very high !**

RBE of neutrons : energy dependence

- RBE neutron energy dependence for dicentric chromosome aberrations (low dose RBE_M and RBE 1 Gy)



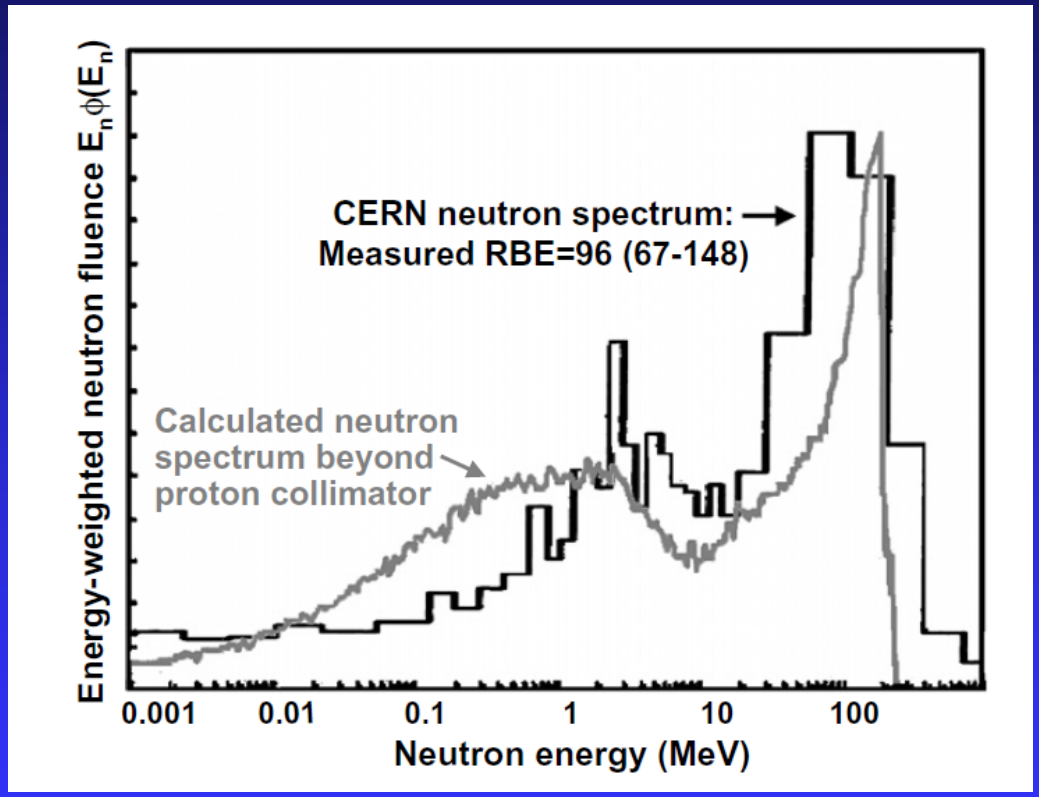


➔ RBE of neutrons strongly energy dependent (ICRP publication 92) !

➔ RBE secondary neutrons proton therapy (high energy) expected to be lower than RBE fission neutrons (1-2 MeV) (Figure right: n spectrum Zheng et al. 2008)

RBE of secondary neutrons proton therapy

- Only data available for dicentrics for neutrons from CERN with similar spectrum as secondary neutrons proton therapy MD Anderson (Brenner and Hall, 2008)



➔ RBE for dicentrics: 96!!!

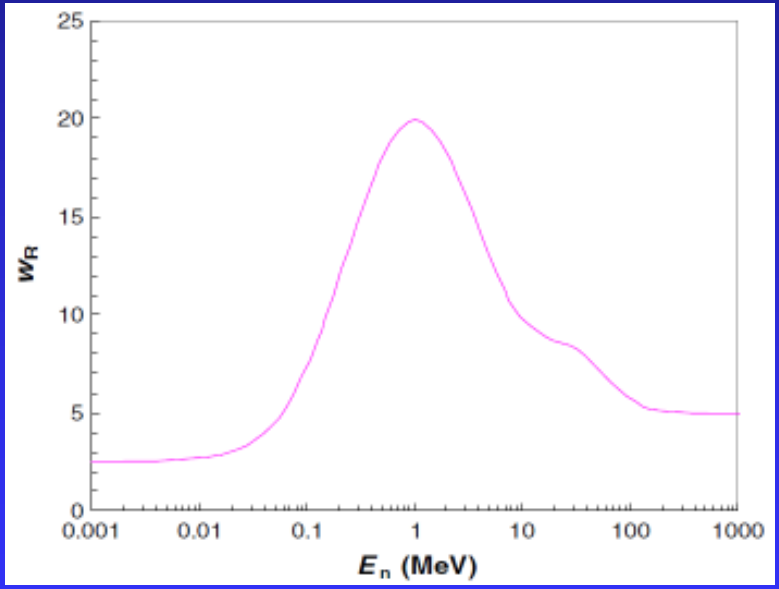
➔ Estimation RBE Brenner and Hall (2008) : 25 with uncertainty factor of 4

Energy dependence radiation weighting factor w_R according to ICRP publication 92 (2003)

- Equivalent dose for organs and tissues H_T (Sv) can be deduced from absorbed dose D_T (Gy) by taking into account the radiation weighting factor w_R

$$H_T = w_R D_T$$

- w_R deduced from RBE data for different biological endpoints by International Commission Radiological Protection



➔ Energy dependence ICRP 92 (2003) results in w_R proton therapy n of 5-10

➔ w_R ICRP 92 << w_R of 25 of Brenner and Hall (2008) based on CA data

Production of secondary neutrons in passive scattering proton therapy (PPT)

- Secondary neutrons produced by interaction of high energy protons with components of beam line
- Largest source of neutrons is generally final collimator located close to the patient

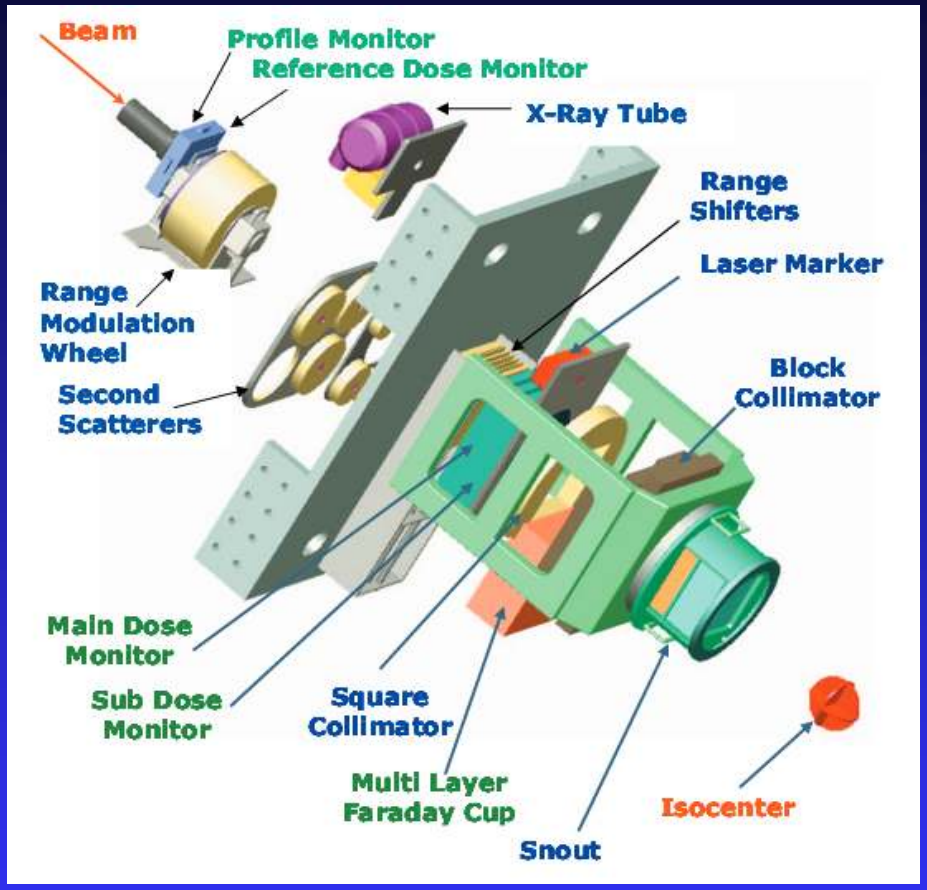
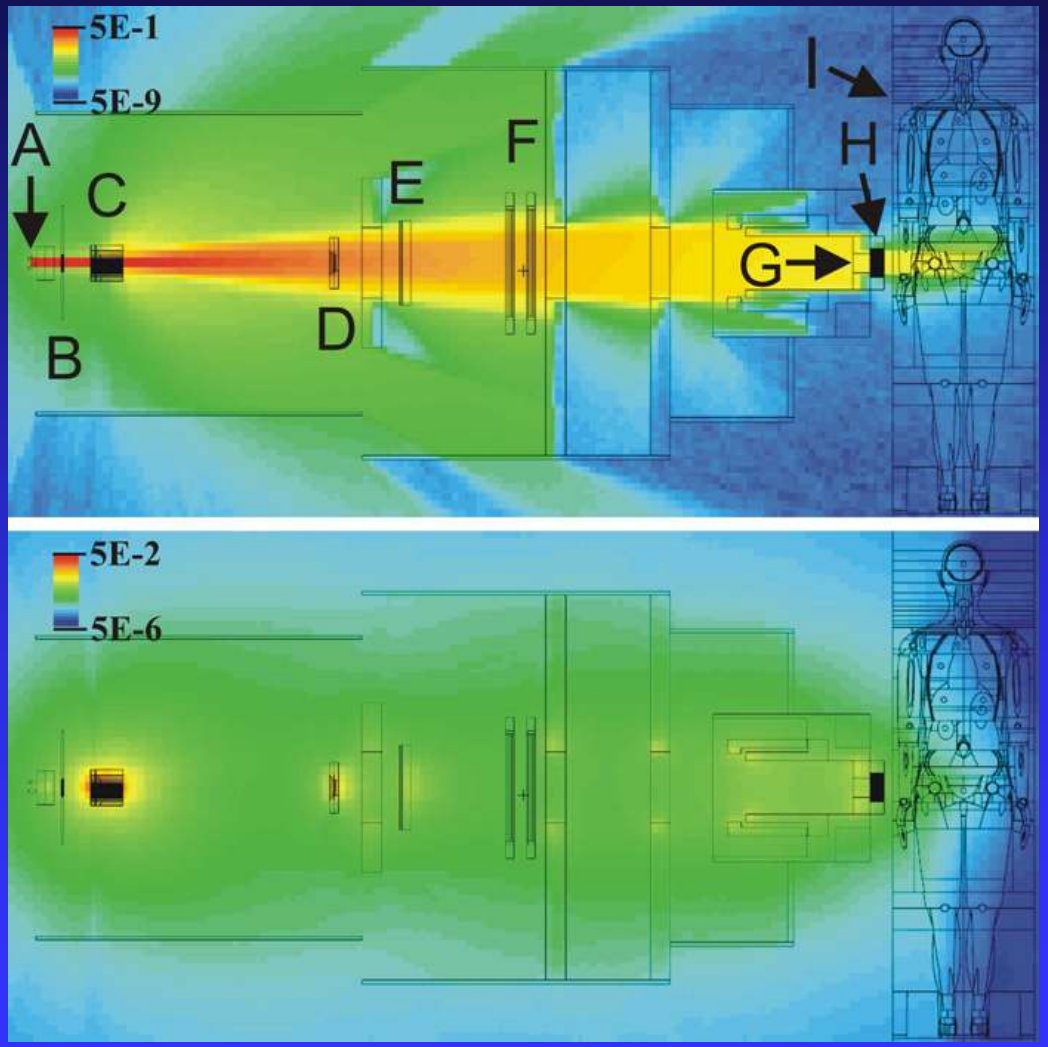


Figure: Smith et al Medical Physics (2009)

- Also secondary neutrons produced internally in patient's tissue hit by the proton beam

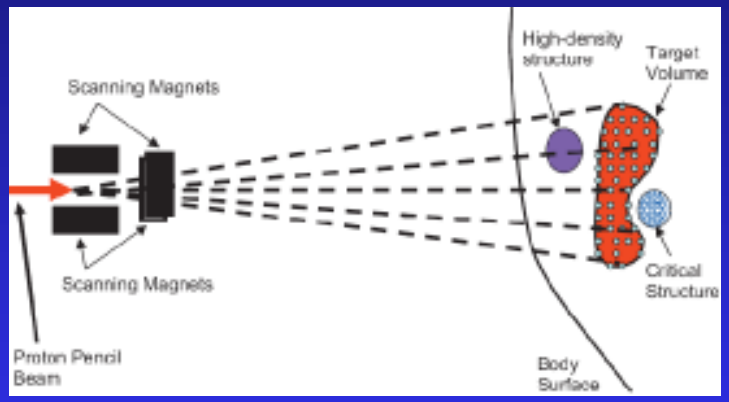
Calculated proton and secondary neutron flux for a PPT proton beam treatment of prostate cancer (Fontenot et al PMB 2008)

- Proton flux
- Neutron flux



Proton therapy systems with pencil beam scanning (PBS)

- Scanning magnets produce lateral beam spot scanning
- This modality allows intensity modulated proton therapy (IMPT)



- Secondary neutrons only produced internally in patient's tissue hit by the proton beam

➔ patient's dose and risk related to secondary neutrons less than in passive scattering proton therapy (PPT)

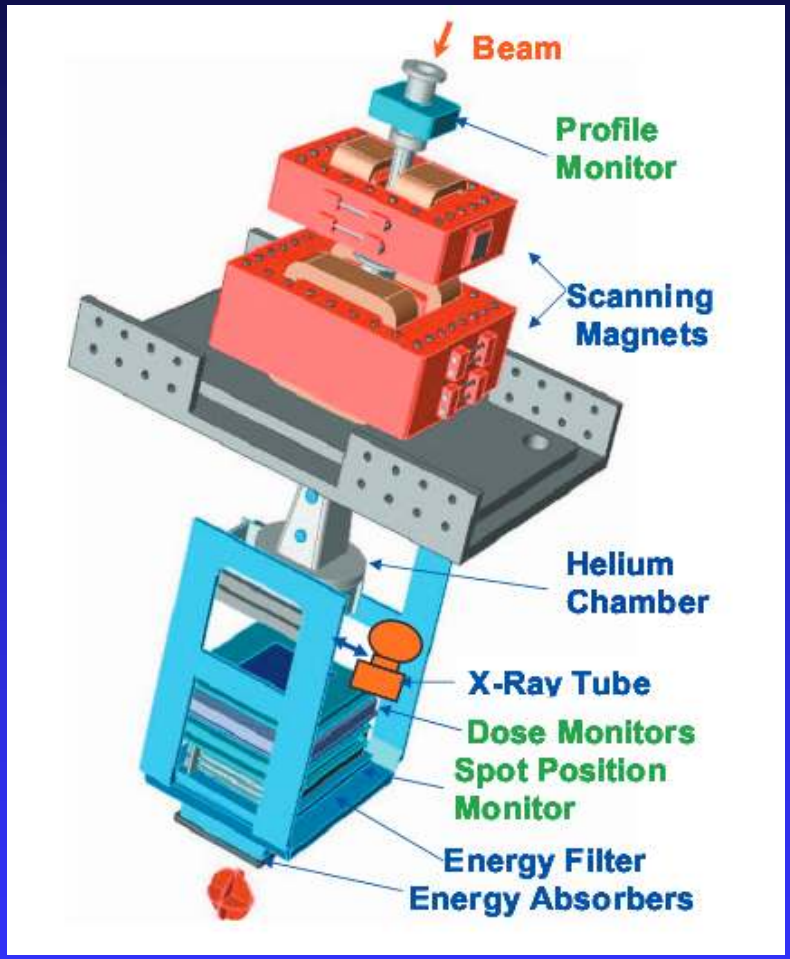
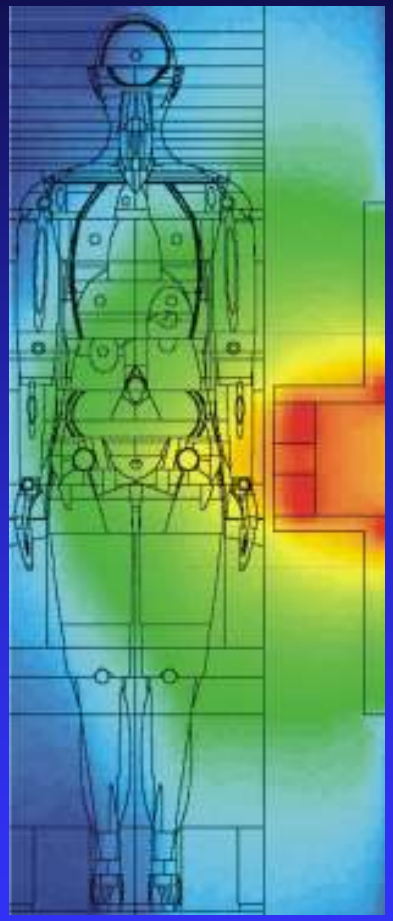


Figure: Smith et al Medical Physics (2009)

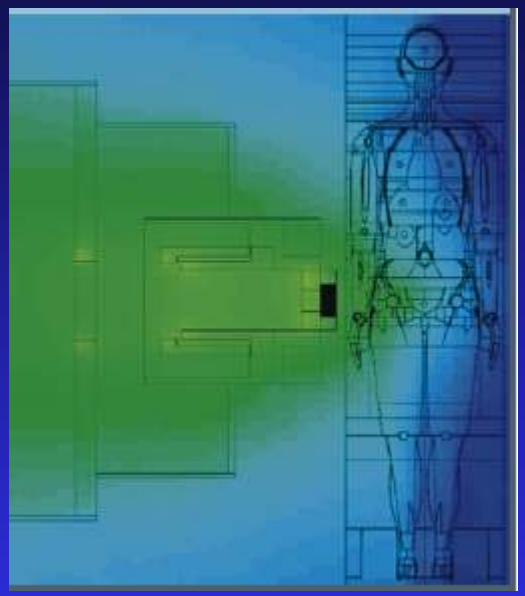
Comparison of neutron flux between passive scattering (PPT) (left) and spot scanning therapy (PBS) (right) (Newhauser PMB 2009)

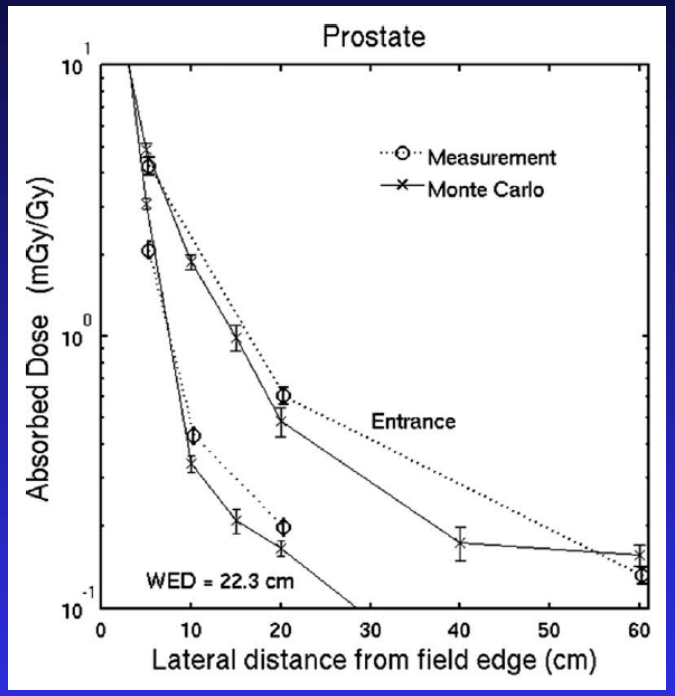


➔ **Both distributions normalised to maximal value within treatment modality**

Equivalent doses and effective dose from neutrons in passively scattered proton therapy for prostate cancer (Fontenot et al PMB 2008)

- Neutron flux



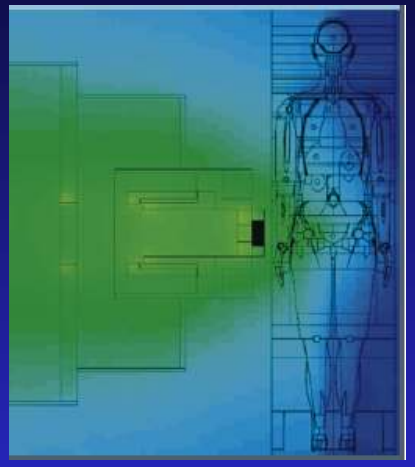


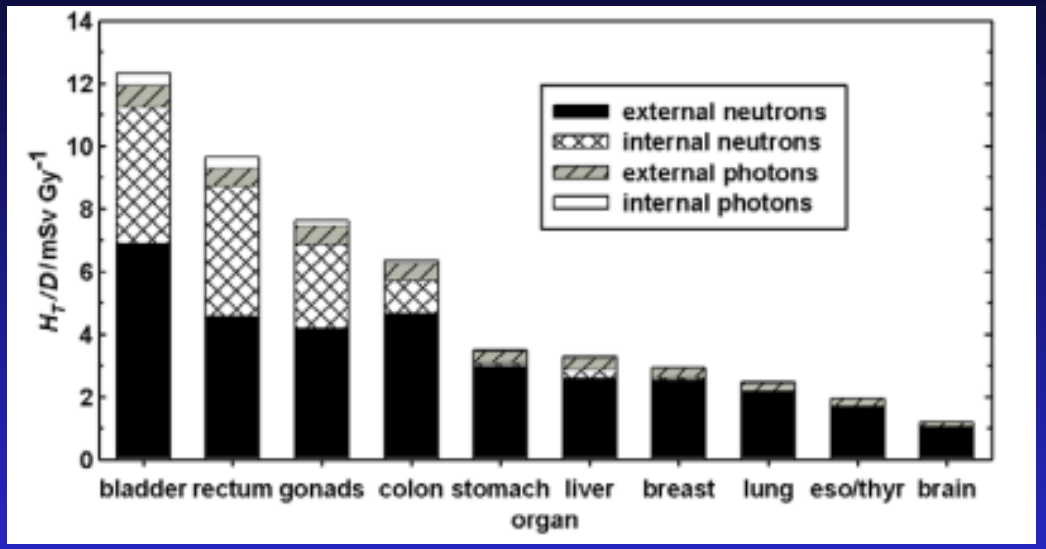
➔ Absorbed dose neutrons stray radiation strongly dependent of lateral distance of field edge and depth in phantom and patient

- Organs and tissues close to treatment field at surface receive highest neutron dose: within 20 cm of field absorbed dose 0.5-5 mGy per Gy therapy dose

Equivalent doses and effective dose from neutrons in passively scattered proton therapy for prostate cancer

(Fontenot PMB 2008)





- Equivalent dose for organs and tissues H_T (mSv) per therapeutic absorbed dose D (Gy). The contribution generated by stray neutron radiation in and outside the patient is presented. Neutron w_R of 6.2 adopted from ICRP 62.

- Effective dose E calculated from H_T with w_T tissue weighting factor

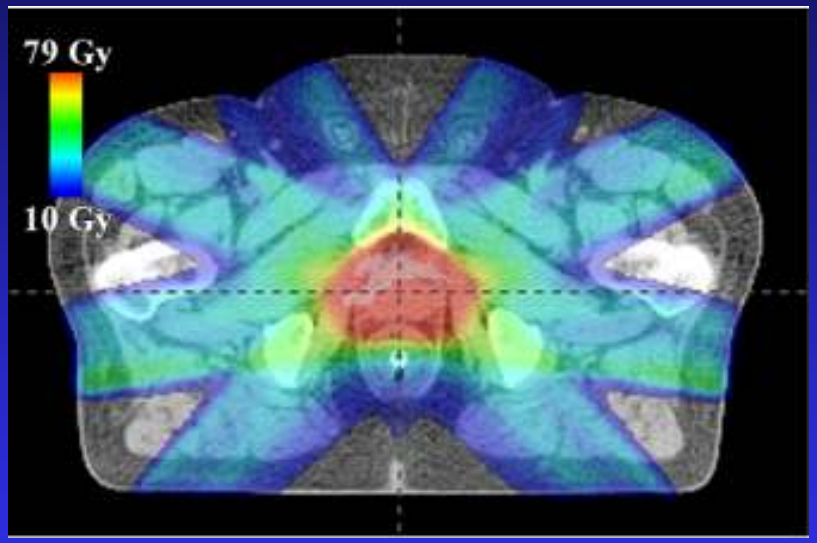
$$E = \sum_T w_T \, H_T$$

➔ E /D = 5.5 mSv/Gy : treatment of 75 Gy results in E = 412 mSv

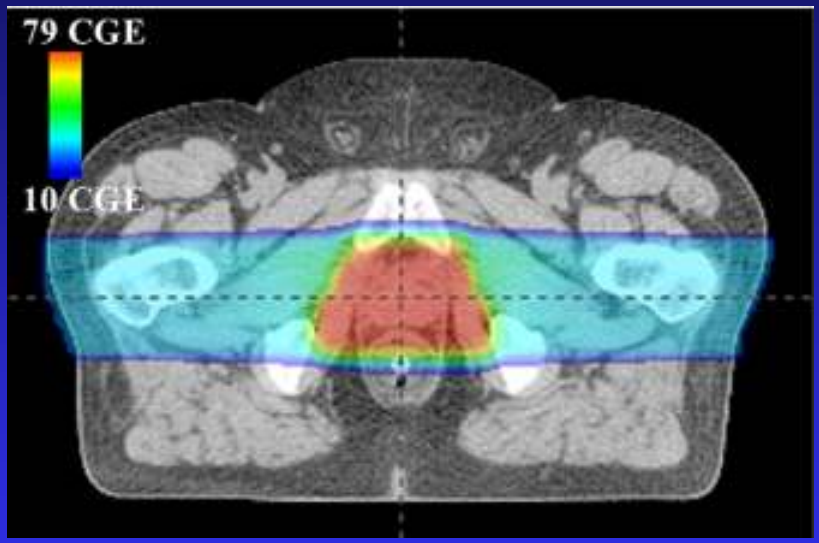
➔ Application of linear-non-threshold (LNT) model yields for 60-70 year age males 0.6 % secondary cancer risk (ICRP 103 2007)

Risk of secondary malignant neoplasms for prostate cancer: comparison of PPT proton therapy and IMRT based on treatment plans MD Anderson Cancer Center (Fontenot et al IJROBP 2009)

- 6 MV IMRT 75.6 Gy



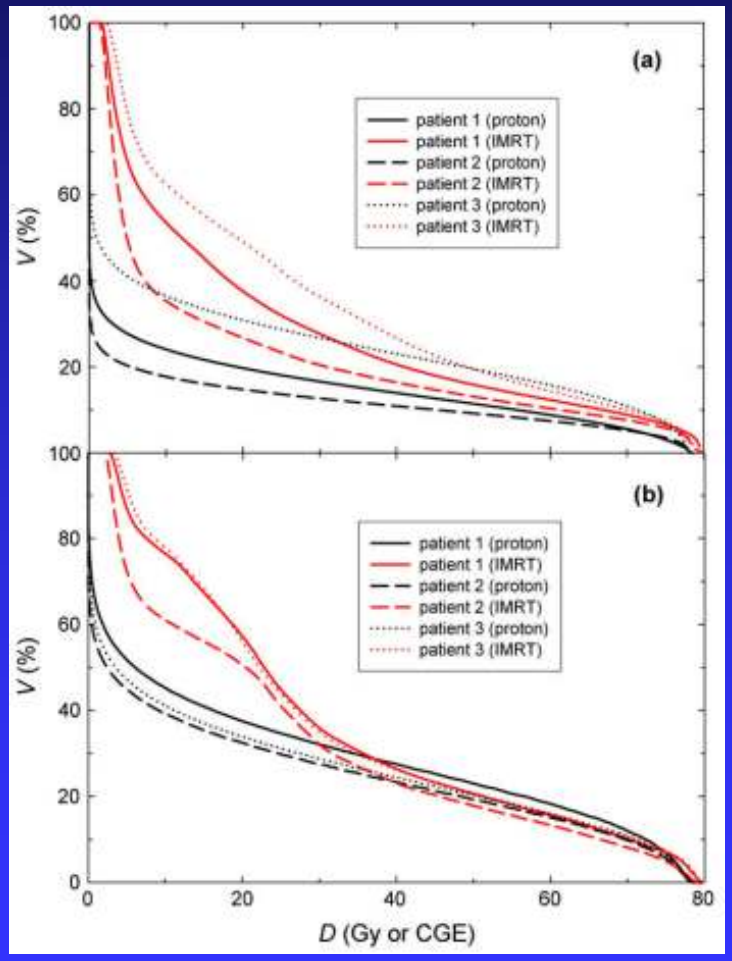
PPT 75.6 CGE (68.7 Gy x 1.1 RBE)



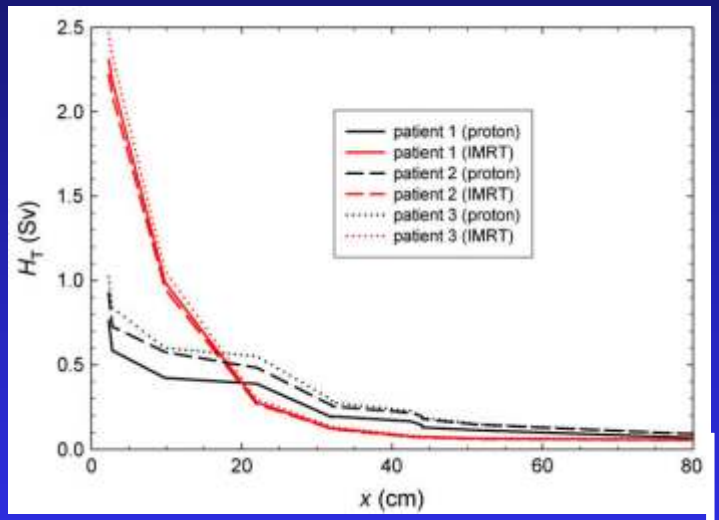
- In both cases total dose given in 42 fractions
- Three patients considered for the study with age range 47-61 years
- Radiation dose to organs at risk for developing a secondary neoplasm was calculated
- Different models for calculating risk for secondary neoplasm applied
- Endpoint : ratio of risk protons versus IMRT

Risk of secondary malignant neoplasms for prostate cancer: comparison of PPT proton therapy and IMRT based on treatment plans MD Anderson Cancer Center (Fontenot IJROBP 2009)

- DVH for bladder (a) and rectum (b)



Equivalent dose from stray radiation as function of distance from isocenter



➔ Proton plans (black lines) provided lower doses at low and intermediate levels in bladder and rectum.

IMRT plans (red lines) provided lower secondary doses in tissues far from the therapeutic fields (neutrons in PPT !)

Risk models for estimation of secondary cancer risk

- For each organ or tissue an organ-specific risk coefficient R_T can be deduced from epidemiological studies as the A-bomb survivor lifespan study (LSS)

$$R_T = \frac{O - E}{EH_T}$$

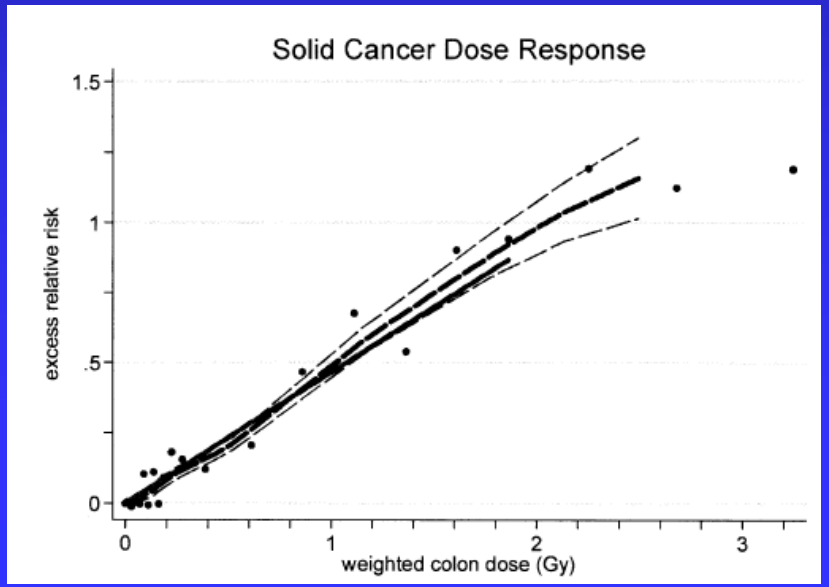
With O incidence or mortality of malignancies related to tissue T in population with equivalent dose to tissue T, H_T, and E incidence or mortality in matched non-exposed control population.

R_T values can be found in BEIR VII committee reports

- The excess relative risk, ERR, for a radiation-induced cancer developing in tissue T receiving an equivalent dose of H_T is given by

$$ERR_T = H_T \times R_T$$

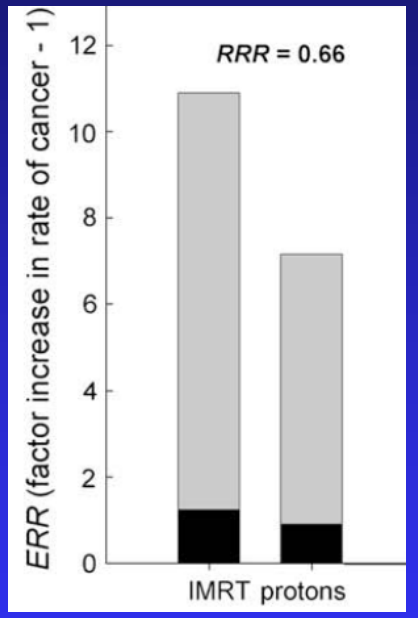
LSS (survivors A bomb) data for colon cancer point to LNT model up to 2 Gy



Risk of secondary malignant neoplasms for prostate cancer: comparison of PPT proton therapy and IMRT based on treatment plans MD Anderson Cancer Center (Fontenot IJROBP 2009)

- For the linear-no-threshold (LNT) risk model with linear extrapolation of the R_T to high doses, ERR_T can be obtained by summing voxel by voxel over all N voxels of the tissue:

$$ERR_T = \frac{1}{N}\sum_{i=1}^{N}(H_{Ti} \times R_T)$$



- The quantity "ratio of excess relative risk" RRR quantifies risk for a secondary malignancy after proton therapy relative to IMRT:

$$RRR = \frac{ERR_{proton}}{ERR_{IMRT}}$$

- The LNT model leads to a RRR of 0.66

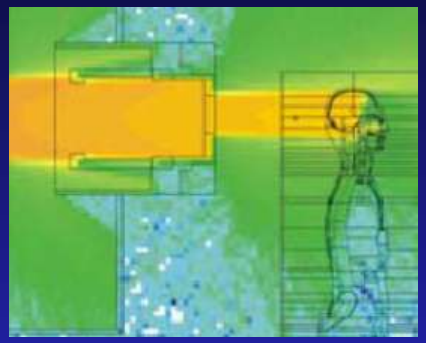
➔ In field organs especially bladder lead to 90 % of total ERR

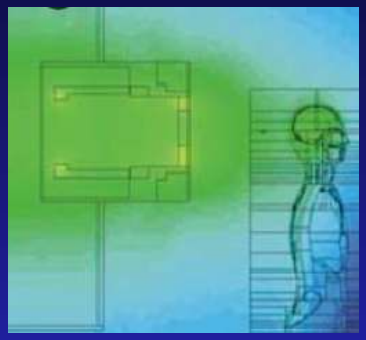
➔ Bone marrow is dominant out of field

➔ Conclusion holds also for other dose-risk models but depends strongly on adopted w_R for neutrons: 6.2 (ICRP 62)

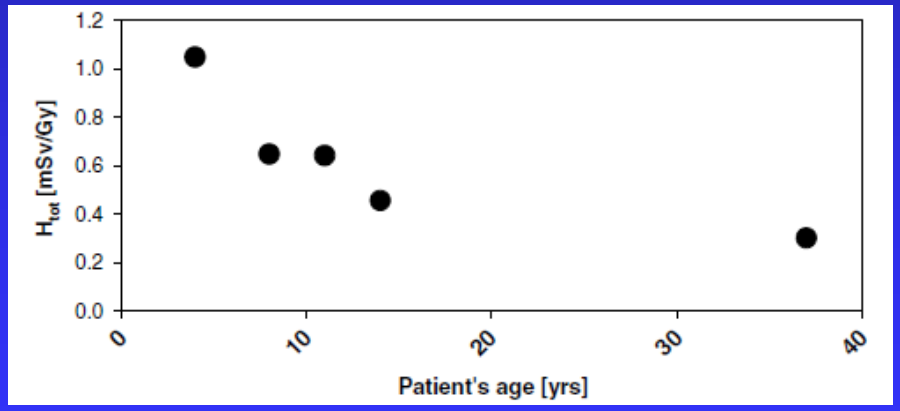
Neutron equivalent doses for proton therapy of intracranial tumours in children (Jarlskog et al PMB 2008)

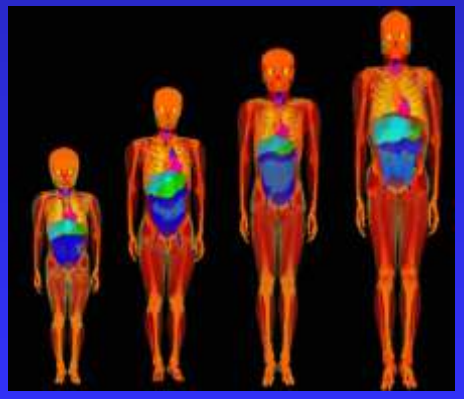
- Representation of proton and neutron fluence for cranial field in PPT (Newhauser PMB 2009) :





- For paediatric applications neutron equivalent dose to organs and tissues strongly dependent on patient age, related to the lateral distance to the field.

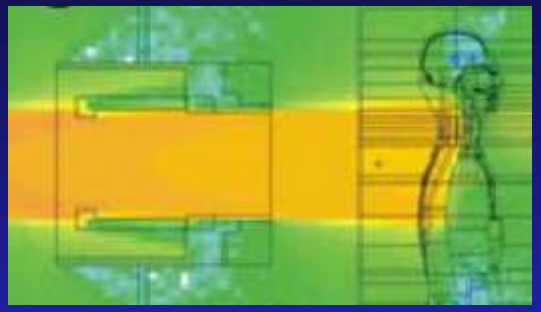


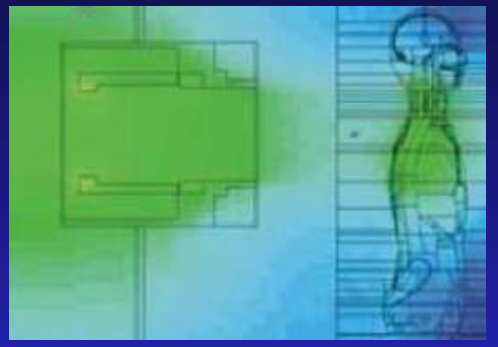


➔ Organ equivalent dose/Gy tumour averaged over the organs contributing to secondary malignancies versus age (average aperture 3, 6, 9 cm)

Risk of secondary malignant neoplasms due to out of field doses for spine fields in a 8 year old female patient: comparison of PPT proton therapy and IMRT (Athar et al Radiother & Oncology 2011)

- Representation proton and neutron fields superior spinal field (Newhauser PMB 2009)

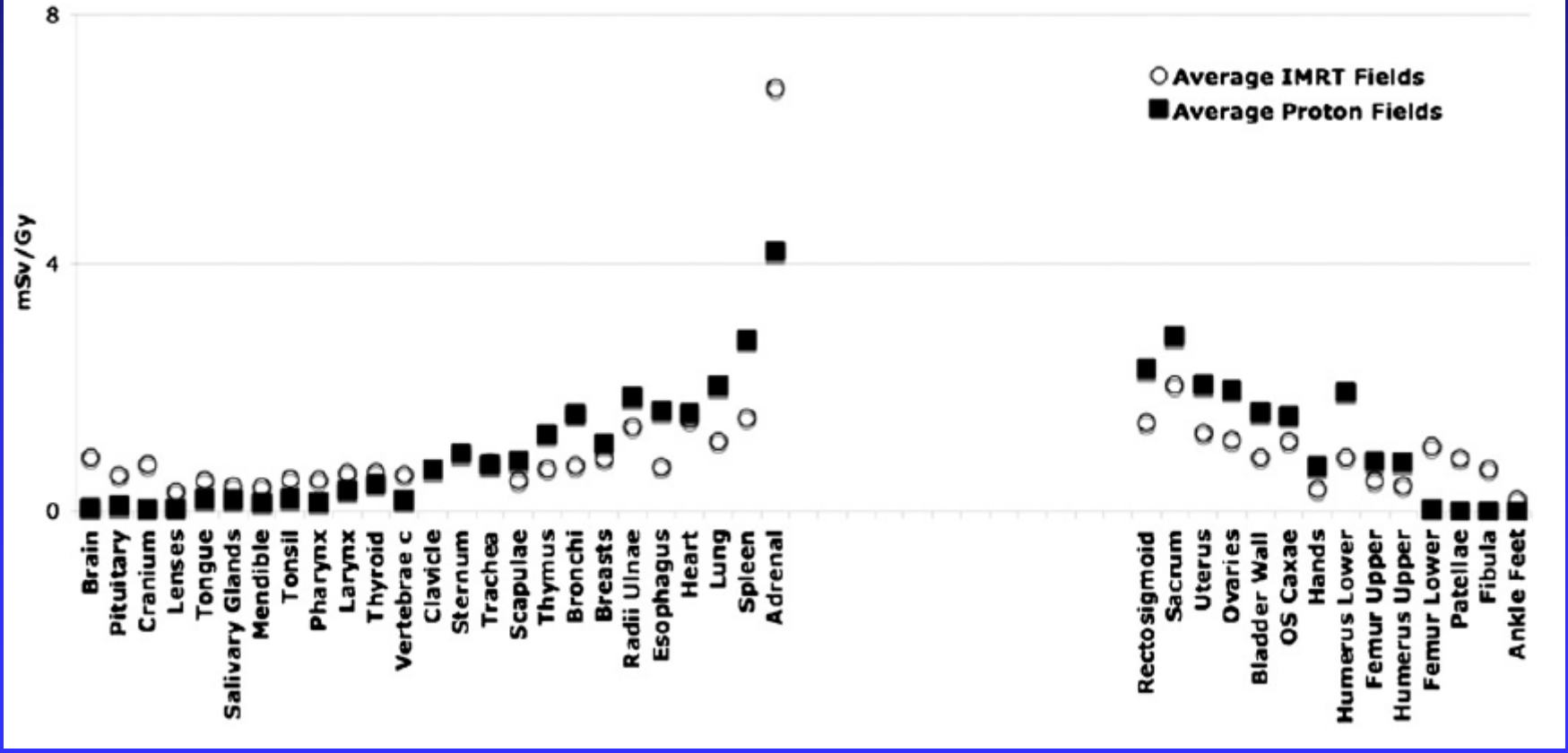




- PPT proton therapy: beam energy at treatment head entrance 196 MeV for 7.5 cm depth and 178 MeV for 10 cm depth; aperture diameters 3, 6, 9 cm
- 6 MV IMRT Varian Linac (2100 Clinac) same field diameters and gantry angle as protons ;
- Proton and IMRT doses normalized to the dose to water in 1.5 cm radius sphere at depth of center of SOBP . One gantry angle geometry.
- MC dose calculations for IMRT (MCNPX) and for protons (Geant4).
- Conversion from absorbed to equivalent dose for neutrons using $w_R = 6.2$ (ICRP 92)
- Simulation for 8 year old female superior spine field

Risk of secondary malignant neoplasms due to out of field doses for spine fields in a 8 year old female patient: comparison of PPT proton therapy and IMRT (Athar Radiotherapy & Oncology 2011)

- Out of field photon (○) and neutron equivalent doses (■) averaged over the three field sizes



Risk of secondary malignant neoplasms due to out of field doses for spine fields in a 8 year old female patient: comparison of PPT proton therapy and IMRT (Athar Radiotherapy & Oncology 2011)

- For the important organs relatively close to the field edge (< 25 cm) the dose due to neutrons in proton therapy is higher than the scattered photon dose in IMRT. Tissues at larger distances receive very low dose with balance is in favour of proton therapy
- For female patients secondary breast cancer is a point of attention. For a field size of 9 cm out of field breast doses are 1.3 mSv/Gy for IMRT and 1.2 mSv/Gy for PPT proton therapy:

  ➔ IMRT and protons same breast cancer risk
- Larger treatment volumes result in more patient scatter but the treatment head contribution decreases with treatment volume as there is less scattering material in the beam path for both IMRT and PPT protons

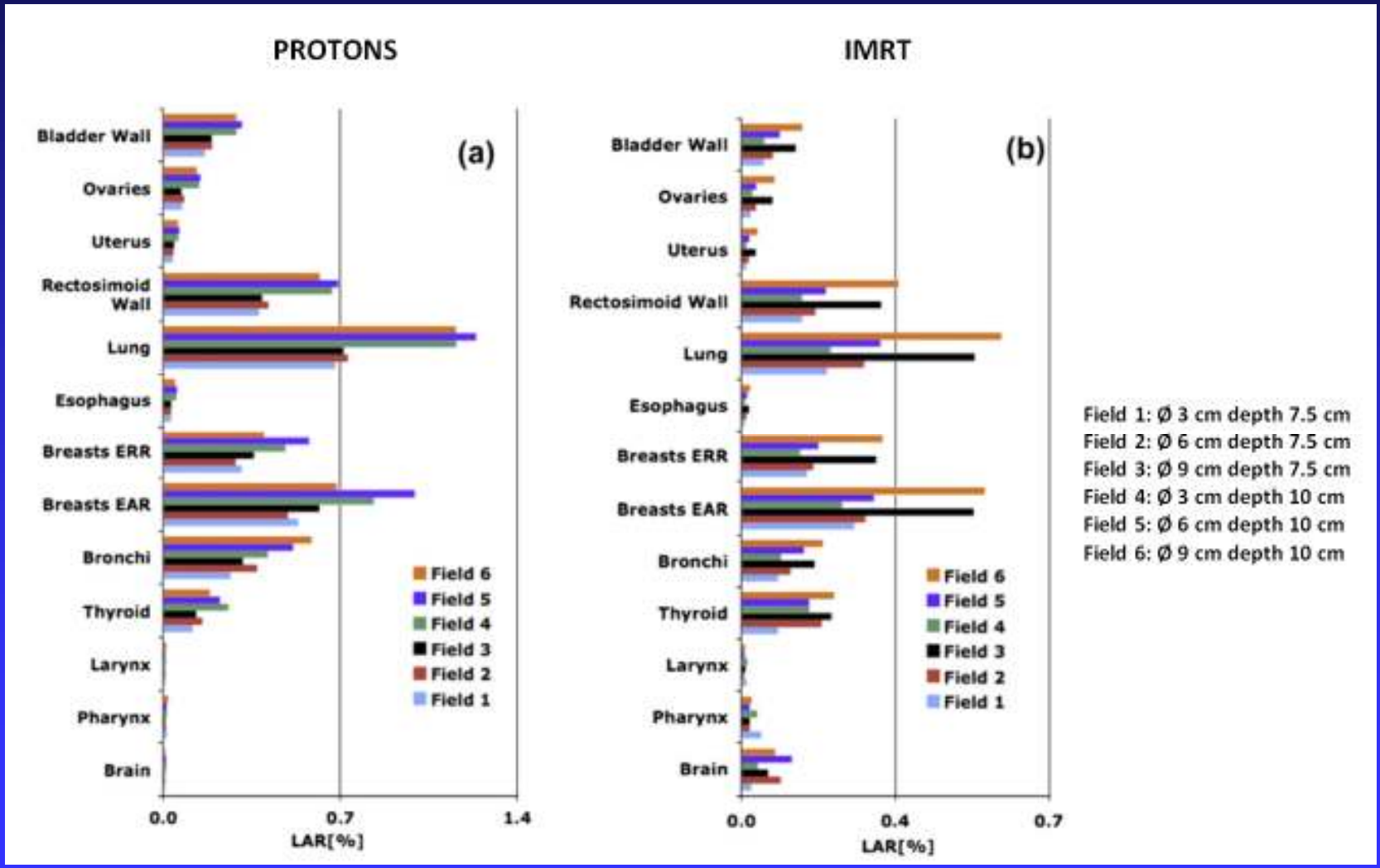
  ➔ For protons both effects cancel out for organs close to the field edge; for organs at larger distances neutron doses decrease with increasing treatment volume
- All calculations assume a w_R of 6.2

Risk of secondary malignant neoplasms due to out of field doses for spine fields in a 8 year old female patient: comparison of PPT proton therapy and IMRT (Athar et al Radiother & Oncology 2011)

- The lifetime attributable risk (LAR) was deduced from the calculated organ doses for a 54 Gy (Gy[RBE]) treatment in a 8 year old female according to the BEIR VII report (2006). LAR was calculated up to the age of 100 years.
- For breast cancer risk the additive excess absolute risk (EAR) model and the multiplicative excess relative risk (ERR) model were applied separately.
- The dose and dose rate effectiveness factor (DDREF) is the ratio between the risk or radiation detriment per unit equivalent dose for high doses and/or dose rates and that for low doses and dose rates. For IMRT a DDREF value of 1.5 was adopted, for neutrons DDREF = 1.
- In addition a calculation was also performed for scanning beam proton therapy based on the neutrons produced internally in the patient

Risk of secondary malignant neoplasms due to out of field doses for spine fields for a 54 Gy treatment in a 8 year old female patient: comparison of PPT proton therapy and IMRT

(Athar et al Radiotherapy & Oncology 2011)



Risk of secondary malignant neoplasms due to out of field doses for spine fields for a 54 Gy treatment in a 8 year old female patient: comparison of proton therapy and IMRT

(Athar Radiotherapy & Oncology 2011)

- Most critical organs are breasts, lungs, rectosigmoid wall, bladder wall.

Organ	LAR PPT (%)	LAR PBS(%)	LAR IMRT(%)	Baseline (%)
Breast EAR	0.68	0.13	0.55	13
Breast EER	0.40	0.07	0.32	13
Lungs	1.16	0.16	0.59	6.7
rectosigm	0.62	0.10	0.36	5.4
Bladder	0.29	0.04	0.14	1.3

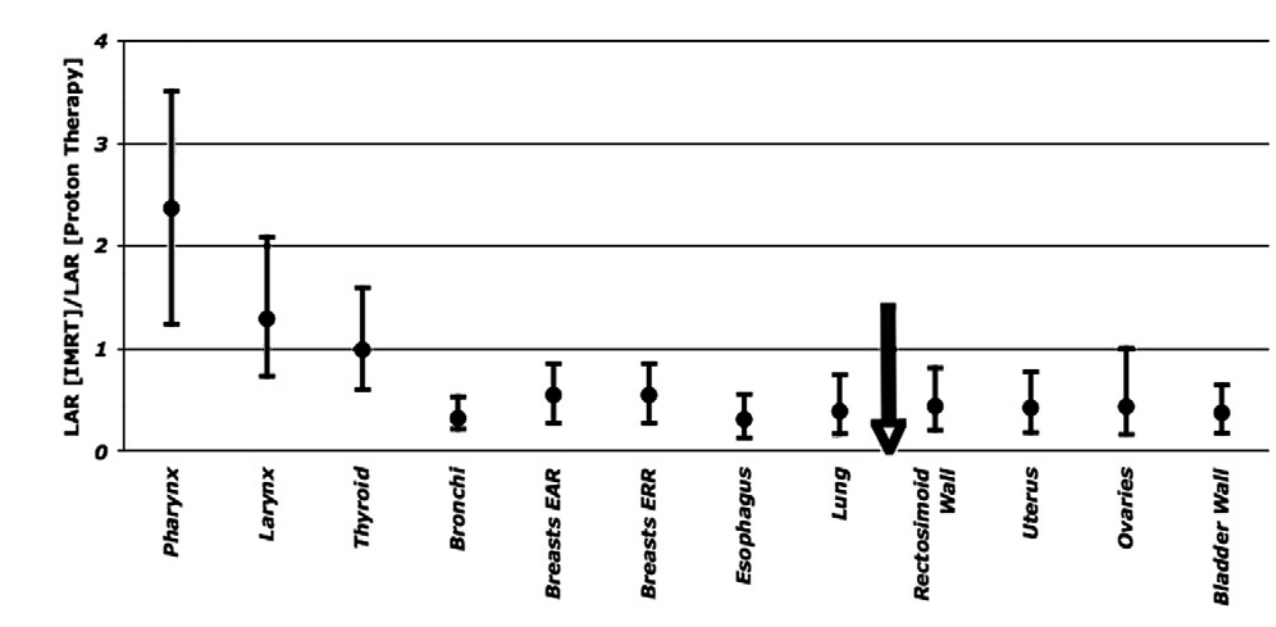
➔ Risks for secondary malignancies are well below the baseline risks

➔ LAR for scanning beam proton therapy drastically lower than for passive scattered proton therapy and IMRT

Risk of secondary malignant neoplasms due to out of field doses for spine fields for a 54 Gy treatment in a 8 year old female patient: comparison of proton therapy and IMRT

(Athar Radiotherapy & Oncology 2011)

- Ratio of LAR values from IMRT and proton therapy for spine fields 54 Gy treatment. Arrow indicates location of the treatment field.



➔ IMRT offers advantage for important organs out of field close to the target.

➔ When patient age increases out-of-field risks shift more in favor of protons

Risk of secondary malignant neoplasms in pediatric patient treatments of central spine and cranium : comparison of 6 MV IMRT and proton therapy conclusions (Athar et al Rad & Onc 2011)

- After averaging over relevant organs risks of secondary cancer from out-of-field doses risks related to IMRT are less than for PPT proton therapy.
- However within the radiation fields the integral dose to the patient is 2-3 times less in PPT proton therapy compared to IMRT, compensating for the difference in the out-of-field organs risk.
- Without any doubt pencil beam scanning proton (PBS) beams are the best choice from viewpoint of secondary cancer risk
- Furthermore the difference in risk estimation between PPT proton therapy and IMRT is determined by the choice of the biological factors DDREF for photon therapy and w_R for proton induced neutrons (LAR values for PPT can be 10 times higher) !

➔ For a more reliable determination of LAR values of proton therapy and comparison between protons and IMRT a thorough study of w_R for relevant biological endpoints is indicated as well as the availability of epidemiological data.

Epidemiological study : incidence of secondary malignancies among patients treated with protons versus photon radiation
(C.S. Chung et al. IJROBP 2013)

Objective: Comparison of incidence of secondary malignancies in patients treated with proton therapy with a population-based cohort of matched patients treated with photons.

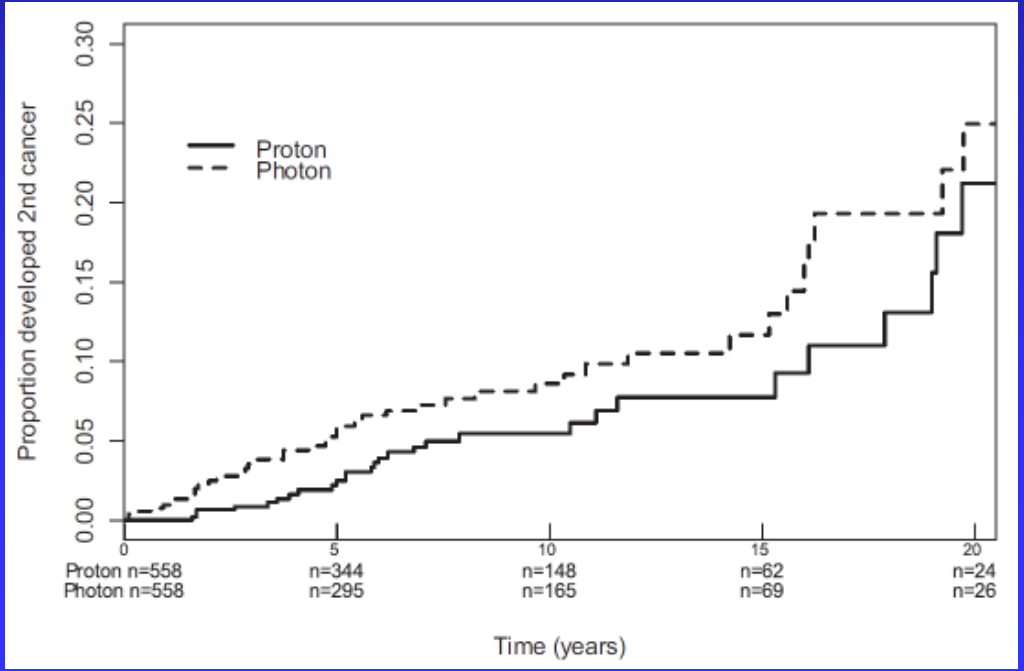
Cohorts:

- 558 patients treated with protons at the Harvard Cyclotron, Cambridge, Massachusetts for different types of malignancies (CNS 32%, H&N 24%, prostate 33%,..) in period 1973-2001
- 558 patients treated with photons matched by age of treatment, sex, cancer histology and site, year of treatment and selected from the SEER cancer registry.
- Median age of treatment was 59 years in each cohort; only 8% of patients were pediatric patients
- 70 % male, 30% female.
- Median follow up time : 6.7 and 6.0 years in proton and photon cohorts

Epidemiologial study : incidence of secondary malignancies among patients treated with protons versus photon radiation
(C.S. Chung et al. IJROBP 2013)

Results:

- # secondary malignancies: 29 patients (5.2%) for protons versus 42 patients (7.5%) for photons.
- Incidence rate of secondary malignancies per 1000 person-years in follow-up period: 6.9 for protons versus 10.3 for photon therapy
- Cumulative incidence curves for secondary cancer



Epidemiological study : incidence of secondary malignancies among patients treated with protons versus photon radiation
(C.S. Chung et al. IJROBP 2013)

Results:

- Any of the pediatric patients treated with protons or photons developed secondary cancer. Remark: follow up period very short !
- Secondary malignancies in the prior field of radiation: 3 out of 29 patients (10%) for protons versus 7 out of 42 patients (17%) for photons.

  ➔ Reduction of secondary cancers for protons mostly outside the field
- Adjusted hazard ratio for development of secondary cancer using the Cox proportional hazards model adjusting for age at treatment and sex is for protons compared to photons

  0.52 (95% CI 0.32-0.85) with p 0.009

  ➔ Proton therapy seems to be more safe with respect to secondary cancers
- Preliminary study ! : longer follow up and more epidemiological studies comparing proton and photon therapy are needed

Conclusions

- **Risk for secondary cancers is without any doubt lowest for pencil beam scanning (PBS) proton therapy**
- **As well studies based on treatment plans as recent epidemiological information point to lower risk of secondary cancers in PPT proton therapy compared to IMRT in adult patients. Less clear in paediatric patients.**
- **To confirm these early observations more scientific work is needed :**

  ➔ direct w_R determination for proton therapy neutrons for relevant biological endpoints related to cancer risk

  ➔ study of RBE for protons: need to revisit the generic RBE of 1.1 at the end of the proton path (end of Bragg peak)

  ➔ dose-volume effects in normal tissue response : can the experience of photon therapy be extrapolated to protons ?

➔ Subjects of a postdoc research programme (Dr Charlot Vandevoorde) of the Ghent group with the proton facility of iThemba LABS (SA), started 2016.


Thanks for your attention !!